

THAT WHICH IS CLAIMED IS:

1. A liposome containing an active agent, said liposome having a gel-phase lipid bilayer membrane comprising phospholipid and a surface active agent,
5 wherein phospholipids are the primary lipid source for the lipid bilayer membrane and wherein surface active agent is contained in the bilayer membrane in an amount sufficient to increase the percentage of active agent released at the phase transition temperature of the lipid bilayer, compared to that which would occur in the absence of said surface active agent, and wherein the surface active agent is present in the lipid
10 bilayer membrane such that the membrane is stable in the gel-phase.
2. A liposome according to Claim 1, wherein the surface active agent is selected from the group consisting of ⁽¹⁶⁾palmitoyl alcohols, ⁽¹⁸⁾stearoyl alcohols, myristoyl, palmitoyl, stearoyl surfactants, polyethylene glycol-derivatized surfactants,
15 glyceryl monopalmitate, glyceryl monooleate, ceramides, PEG-ceramides, ~~block copolymers~~, therapeutic lipids, glycolipids, bile salts, and mixtures thereof.
3. A liposome according to Claim 1, wherein the surface active agent is lysolipid.
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4. A liposome according to Claim 3, wherein the lysolipid is monopalmitoylphosphatidylcholine (MPPC) monolaurylphosphatidylcholine (MLPC), monomyristoylphosphatidylcholine (MMPC),
25 monostearoylphosphatidylcholine (MSPC), and mixtures thereof.
5. A liposome according to claim 3, wherein phospholipid and lysolipid are contained in said bilayer membrane in a ratio of from 99:1 to 50:50 by molar weight.
6. A liposome according to claim 1, wherein said phospholipid contains
30 saturated acyl groups.
7. A liposome according to claim 3, wherein said phospholipid is dipalmitoylphosphatidylcholine (DPPC) and said lysolipid is monopalmitoylphosphatidylcholine (MPPC).

8. A liposome according to Claim 1, wherein the surface active agent is a dichain phospholipid having a chain length of no greater than C9.

5 9. A liposome according to claim 1, wherein said active agent is entrapped within the liposome interior.

10 10. A liposome according to claim 1, wherein said active agent is entrapped within the lipid bilayer membrane.

11. A liposome according to claim 1 having a diameter of from about 50 nanometers to about 400 nanometers.

12. A liposome according to claim 1, wherein the liposome bilayer further comprises phospholipid derivatized with a hydrophilic polymer.

13. A liposome according to claim 12, wherein said hydrophilic polymer is selected from the group consisting of polyethylene glycol, polylactic acid, polyglycolic acid, copolymers of polylactic acid and polyglycolic acid, polyvinyl alcohols, polyvinylpyrrolidone, dextrans, oligosaccharides, and mixtures thereof.

14. A liposome according to claim 1, wherein said active agent is a pharmacologically active agent, a flavor agent, a diagnostic agent, or a nutritional agent.

15. A liposome according to claim 1, wherein said active agent is a pharmacologically active agent selected from the group consisting of antineoplastic agents, anti-inflammatory agents, immunosuppressive agents, antibiotic agents, and anti-infective agents.

16. A liposome according to Claim 1, wherein the active agent is an antihistamine.

17. A liposome according to claim 1, wherein said active agent is selected from the group consisting of methotrexate, doxorubicin, epirubicin, daunorubicin, vincristine, vinblastine, etoposide, ellipticine, camptothecin, paclitaxel, docetaxol, cisplatin, prednisone, methyl-prednisone, navabene, and ibuprofen.

5 18. A liposome according to claim 1, wherein said active agent is paclitaxel.

10 19. A liposome according to claim 1, wherein said active agent is camptothecin.

20. A liposome according to claim 1, wherein said active agent is doxorubicin.

15 21. A liposome containing an active agent, said liposome having a gel-phase lipid bilayer membrane comprising phospholipid and lysolipid, wherein phospholipids are the primary lipid source for the lipid bilayer membrane and wherein lysolipid is contained in the bilayer membrane in an amount sufficient to increase the percentage of active agent released at the phase transition temperature of the lipid bilayer, compared to that which would occur in the absence of said lysolipid, wherein phospholipid and lysolipid are contained in said bilayer membrane in a ratio of from 99:1 to 50:50 by molar weight.

25 22. A liposome according to Claim 21, wherein the lysolipid is selected from the group consisting of monopalmitoylphosphatidylcholine (MPPC), monolaurylphosphatidylcholine (MLPC), monomyristoylphosphatidylcholine (MMPC), monostearoylphosphatidylcholine (MSPC), and mixtures thereof.

30 23. A liposome according to claim 21, wherein phospholipid and lysolipid are contained in said bilayer membrane in a ratio of from 99:1 to 70:30 by molar weight.

24. A liposome according to claim 21, wherein said phospholipid contains saturated acyl groups.

25. A liposome according to claim 21, wherein said phospholipid is
5 dipalmitoylphosphatidylcholine (DPPC) and said lysolipid is monopalmitoylphosphatidylcholine (MPPC).

26. A liposome according to claim 21, wherein said active agent is entrapped within the liposome interior.

27. A liposome according to claim 21, wherein said active agent is entrapped within the lipid bilayer membrane.

28. A liposome according to claim 21 having a diameter of from about 50
15 nanometers to about 400 nanometers.

29. A liposome according to claim 21, wherein the liposome bilayer further comprises phospholipid derivatized with a hydrophilic polymer.

30. A liposome according to claim 29, wherein said hydrophilic polymer is
20 selected from the group consisting of polyethylene glycol, polylactic acid, polyglycolic acid, copolymers of polylactic acid and polyglycolic acid, polyvinyl alcohols, polyvinylpyrrolidone, dextrans, oligosaccharides, and mixtures thereof.

31. A liposome according to claim 21, wherein said active agent is a
25 pharmacologically active agent, a flavor agent, a diagnostic agent, or a nutritional agent.

32. A liposome according to claim 21, wherein said active agent is a
30 pharmacologically active agent selected from the group consisting of antineoplastic agents, anti-inflammatory agents, immunosuppressive agents, antibiotic agents, and anti-infective agents.

33. A liposome according to Claim 21, wherein the active agent is an antihistamine.

5 34. A liposome according to claim 21, wherein said active agent is selected from the group consisting of methotrexate, doxorubicin, epirubicin, daunorubicin, vincristine, vinblastine, etoposide, ellipticine, camptothecin, paclitaxel, docetaxol, cisplatin, prednisone, methyl-prednisone, navabene, and ibuprofen.

10 35. A liposome according to claim 21, wherein said active agent is paclitaxel.

36. A liposome according to claim 21, wherein said active agent is camptothecin.

15 37. A liposome according to claim 21, wherein said active agent is doxorubicin.

38. A liposome containing an active agent, said liposome having a gel-phase lipid bilayer membrane comprising phospholipid and a second component, 20 wherein phospholipids are the primary lipid source for the lipid bilayer membrane and wherein said second component is contained in the bilayer membrane in an amount sufficient to increase the percentage of material to be released at the phase transition temperature of the lipid bilayer, compared to that which would occur in the absence of the second component, and wherein the second component is present in the lipid 25 bilayer membrane such that the membrane is stable in the gel-phase, said material to be released from the liposome being the second component or a third component which is entrapped within the liposome interior or associated with the lipid bilayer membrane.

30 39. A liposome according to claim 38, wherein said material is the second component.

40. A liposome according to claim 39, wherein the second component is an active agent.

41. A liposome according to claim 40, wherein the active agent is a pharmacologically active agent selected from the group consisting of ceramides, and platelet activating factor.

42. A liposome according to claim 38, wherein said material is the component which is entrapped within the liposome interior or associated with the lipid bilayer membrane.

43. A method of making liposomes containing an active agent entrapped within the liposome interior space, comprising:

- a) preparing a phospholipid film containing surface active agent;
- b) hydrating said phospholipid film with an aqueous preparation containing an active agent and surface active agent to produce liposomes, said surface active agent contained in the aqueous preparation in an amount sufficient to provide an equilibrating amount of surface active agent in the interior of said liposomes; and then
- c) cooling said liposomes produced in (b) to produce a liposome with a gel-phase lipid bilayer;

wherein surface active agent is contained in the liposome membrane in an amount sufficient to increase the percentage of active agent released at the phase transition temperature of the liposome membrane, compared to that which would occur in the absence of said surface active agent.

44. A method according to claim 43 wherein the surface active agent is selected from the group consisting of palmitoyl alcohols, stearyl alcohols, palmitoyl surfactants, stearyl surfactants, myristoyl surfactants, polyethylene glycol, glyceryl monopalmitate, glyceryl monooleate, ceramides, PEG-ceramides, therapeutic lipids, and mixtures thereof.

45. A method according to claim 43 wherein the surface active agent is lysolipid and wherein said lipid bilayer membrane contains from 5 mole % to 50 mole % lysolipid.

5 46. A method according to claim 43, wherein said active agent is entrapped within the liposome interior.

47. A method according to claim 43, wherein said active agent is entrapped within the lipid bilayer membrane.

10 48. A method according to claim 43, wherein said liposome bilayer further comprises phospholipid derivatized with a hydrophilic polymer.

49. A method according to claim 48, wherein said hydrophilic polymer is selected from the group consisting of polyethylene glycol, polylactic acid, polyglycolic acid, copolymers of polylactic acid and polyglycolic acid, polyvinyl alcohols, polyvinylpyrrolidone, dextrans, oligosaccharides, and mixtures thereof.

50. A method according to claim 43, wherein said phospholipid is dipalmitoylphosphatidylcholine (DPPC) and said surface active agent is lysolipid which is monopalmitoylphosphatidylcholine (MPPC).

51. A method according to claim 43, wherein said active agent is a pharmacologically active agent, a flavor agent, a diagnostic agent, or a nutritional agent.

52. A method according to claim 43, wherein said active agent is a pharmacologically active agent selected from the group consisting of antineoplastic agents, anti-inflammatory agents, anti-tumor agents, immunosuppressive agents, antibiotic agents and anti-infective agents.

53. A method according to claim 43, wherein said active agent is selected from the group consisting of methotrexate, doxorubicin, epirubicin, daunorubicin,

vincristine, vinblastine, etoposide, ellipticine, camptothecin, paclitaxel, docetaxol, cisplatin, prednisone, methyl-prednisone, and ibuprofen.

5 54. A method according to claim 43, wherein said active agent is paclitaxel.

55. A method according to ~~claim 43~~, wherein said active agent is camptothecin.

10 56. A method according to claim 43, wherein said active agent is doxorubicin.

57. A method for loading active agents into liposomes comprising:

15 a) providing a liposome comprising a gel-phase lipid bilayer, said lipid bilayer comprising phospholipid, wherein said lipid bilayer is present at a temperature below its phase transition temperature; and

b) exposing the lipid bilayer to an active agent such that said active agent passes into the lipid bilayer wherein said method allows for an increase in the percentage of active agent released at the phase transition temperature of the liposome membrane, compared to that which would occur in liposomes produced by another method.

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58. A method according to claim 57 further comprising the step of cooling the liposome to a temperature below the phase transition temperature of the lipid bilayer prior to step a).

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59. A method according to claim 57 wherein the liposome is present in a surrounding liquid medium, and wherein the pH of the surrounding liquid medium is greater than the pH of the interior of the liposome to facilitate loading of the active agent.

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60. A method according to claim 57 wherein the lipid bilayer further comprises a surface active agent.

61. A method according to claim 60 wherein the surface active agent is selected from the group consisting of palmitoyl alcohols, stearoyl alcohols, myristoyl, palmitoyl, stearoyl surfactants, polyethylene glycol-derivatized surfactants, glyceryl monopalmitate, glyceryl monooleate, ceramides, PEG-ceramides, block copolymers, therapeutic lipids, and mixtures thereof.

62. A method according to claim 60 wherein the surface active agent is lysolipid.

63. A method according to claim 62 wherein the lysolipid is selected from the group consisting of monopalmitoylphosphatidylcholine (MPPC), monolaurylphosphatidylcholine (MLPC), monomyristoylphosphatidylcholine (MMPC), monostearoylphosphatidylcholine (MSPC), and mixtures thereof.

64. A method according to claim 60, wherein said phospholipid is dipalmitoylphosphatidylcholine (DPPC) and said surface active agent is lysolipid which is monopalmitoylphosphatidylcholine (MPPC).

65. A liposome containing an active agent, said liposome having a solid-phase membrane comprising a membrane-forming material and a surface active agent, wherein surface active agent is contained in the bilayer membrane in an amount sufficient to increase the percentage of active agent released at the phase transition temperature of the solid-phase membrane, compared to that which would occur in the absence of said surface active agent, and wherein the surface active agent is present in the membrane so as to not destabilize the membrane while the membrane is in the solid phase.